Loss of cell adhesion protein drives esophageal and oral cancers in mice

April 12 2011

Squamous cell cancers of the oral cavity and esophagus are common throughout the world, with over 650,000 cases of oral cancer each year and esophageal cancer representing the sixth most common cause of cancer death in men. Research by University of Pennsylvania School of Medicine investigators has shown that a protein that helps cells stick together is frequently absent or out of place in these cancers, but it's unclear if its loss causes the tumors.

The investigators report that mice engineered to lack this protein, called p120-catenin (p120ctn), in the oral-upper digestive tract develop squamous cell cancers. The data, reported Cancer Cell, settle a 20-year debate and prove that p120ctn is a tumor-suppressor protein. What's more, the tumors that form in this mouse model closely resemble human disease and may point the way to novel therapies and early detection strategies.

"As the mice aged, what we saw was a dramatic evolution of precancer to cancer," says senior author Anil K. Rustgi, MD, the T. Grier Miller Professor of Medicine and Genetics and chief of Gastroenterology. "Both the precancerous growth, called dysplasia, and the cancer look exactly like what we see in humans. This is really exciting because it supports efforts for prevention and early detection, especially in people who drink alcohol and smoke cigarettes excessively and are at high risk for the disease in many regions of the world."

In healthy tissues, p120ctn is part of a protein complex that holds

epithelial cells in tightly packed sheets. When p120ctn (or another of these cell adhesion proteins) is lost, a wide variety of cancers including those in prostate, breast, pancreas, colon, skin, bladder, and the endometrium, can result.

The cells lose their tight cell-cell contacts and can migrate more easily, which likely favors cancer spread and invasion of new cells. However, earlier attempts to test the effects of p120ctn loss on cancer formation were derailed because the animals cannot survive throughout embryonic development or immediately after birth without the protein.

To get around that problem, Rustgi and colleagues used a system called Cre-Lox that allows them to remove a particular gene in only a subset of tissues. In this case, the team deleted p120ctn from the oral cavity, esophagus and forestomach. The mutant animals survived through early development and birth, but by 4 to 6 months, most of the mutant animals had developed precancerous lesions and by 9 to 12 months, 70 percent of the mutant animals had full blown tumors. By contrast, none of the control littermates developed cancer.

The investigators noted that as the lesions developed, the tumor cells secreted inflammatory signals that acted like homing signals for immune cells called immature myeloid cells. These cells, in turn, helped to create a microenvironment that supported tumor growth. In fact, when the researchers blocked recruitment of the immune cells, they saw a dramatic reduction in tumor invasion.

Based on these observations, Rustgi thinks that targeting the immature myeloid cells may reverse or slow tumor grown in humans, although more work needs to be done in animal models before the approach is tested in the clinic.

Rustgi says that the mouse model will help test innovative therapies and

early detection tests. He says that although he was born and raised in the United States, he was influenced by five years he spent as a child in India, where oral cancer is common due to the proportion of the population that chews betel nuts. "I remember, even as a little kid, I would see people with oral lesions," he says. "I didn't know what they were then, but it has always motivated me at a personal level. Esophageal cancer biology has also been a long-standing interest of mine because it affects so many underserved people in the inner cities in the United States."

Provided by University of Pennsylvania School of Medicine